The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks

Catherine V. Hawkyard and Roland J. Koerner*

Department of Medical Microbiology, Sunderland Royal Hospital, Sunderland SR4 7TP, UK

Erythromycin A, the first macrolide, was introduced in the 1950s and after years of clinical experience it still remains a commonly relied upon antibiotic. In the past, pharmacodynamic characteristics of macrolides beyond antimicrobial action such as anti-inflammatory and immune-modulating properties have been of scientific and clinical interest. The function of erythromycin as a prokinetic agent has also been investigated for a range of gastrointestinal motility disorders and more recently within the context of critically ill patients. Prokinetic agents are drugs that increase contractile force and accelerate intraluminal transit. Whilst the anti-inflammatory action may be a desirable side effect to its antibiotic action, using erythromycin A merely for its prokinetic effect alone raises the concern about promoting emergence of macrolide resistance. The objectives of this review article are: (i) to briefly summarize the modes and epidemiology of macrolide resistance, particularly in respect to that found in the Streptococcus species (a potential reservoir for the dissemination of macrolide resistance on the critical care unit); (ii) to discuss in this context the evidence for conditions promoting bacterial resistance against macrolides; and (iii) to assess the potential clinical benefit of using erythromycin A as a prokinetic versus the risks of promoting emergence of macrolide resistance in the clinical setting. We conclude, that in view of the growing weight of evidence demonstrating the potential epidemiological impact of the increased use of macrolides upon the spread of resistance, versus a lack of sufficient and convincing evidence that erythromycin A is a superior prokinetic agent to potential alternatives in the critically ill patient population, at this stage we do not advocate the use of erythromycin A as a prokinetic agent in critically ill patients unless they have failed all other treatment for impaired gastrointestinal dysmotility and are intolerant of metoclopramide. Further large and methodologically robust studies are needed to ascertain the effectiveness of erythromycin A and other alternative agents in the critically ill.

Keywords: modular evolution, non-antimicrobial activities

Introduction

The macrolides are a group of closely related antibiotics, mostly produced from Streptomyces. The most important therapeutic macrolides are characterized by a 14-, 15- or 16-membered lactone ring. Erythromycin consists of a mixture of compounds in which erythromycin A, which has a 14-member lactone ring, is the active macrolide component. Erythromycin, discovered in 1952, was the first macrolide to be introduced into clinical practice. The 14- (including erythromycin, clarithromycin and roxithromycin), 15- (including azithromycin) and 16-membered ring macrolides share a broad spectrum of antimicrobial activity, exhibiting action against Gram-positive and Gram-negative bacteria. Consequently, erythromycin A (and newer macrolides such as clarithromycin, roxithromycin and azithromycin) are used extensively as a major alternative to the use of penicillins and cephalosporins in many countries for the treatment of infections, especially those caused by β-haemolytic streptococci and pneumococci.

However, there has been rapid spread of bacterial resistance within common pathogens; resistance to erythromycin A within Streptococcus pneumoniae and a drop in efficacy of macrolides upon β-haemolytic streptococci such as Streptococcus pyogenes has been recorded worldwide. This has prompted the development of the ketolide group of antibiotics (a semi-synthetic derivative of erythromycin A). The ketolide telithromycin retains activity against isolates resistant to erythromycin A in S. pneumoniae and S. pyogenes.

Macrolides have been found to have pharmacodynamic properties beyond their antimicrobial mode of action. Some of these include anti-inflammatory and immunomodulatory...
effects. These are beyond the scope of this paper to discuss in further detail having already been extensively reviewed. In these clinical situations, it is noteworthy that the macrolides are being used, often primarily, for their antibiotic effect on the diseases and the aforementioned ‘extra-antibiotic’ effects are an addition to this.

More recently, another extra-antibiotic effect of macrolides has been exploited; their function as a gastrointestinal prokinetic. Prokinetic agents are drugs that increase contractile force and accelerate intraluminal transit. Many studies have been carried out in a wide variety of patient populations and disorders, including gastroesophageal reflux in children, diabetic gastroparesis and functional dyspepsia. This has been investigated in erythromycin A and, to a lesser extent, clarithromycin. Only the prokinetic action of erythromycin A has been studied in the critically ill population to date and therefore we concentrate upon this macrolide as a prokinetic in this review, although in terms of macrolide and ketolide consumption (for whatever purpose), we feel that impact on emergence of resistance is likely to be similar whichever group member is used. In contrast to the anti-inflammatory action, which has a desirable association with the indication for an antibiotic, the prokinetic effect has nothing to do with the primary indication of antibiotics. Although the number of studies investigating the use of erythromycin A as a prokinetic in the critical care setting is small, and few of these comprise large sample sizes, there are already authors who advocate the use of macrolides such as erythromycin A purely for its prokinetic properties. This approach has been supported by guidelines recommending or discussing the use of erythromycin A as a means for the prevention of aspiration of gastric content, a feared complication in the intensive care setting. In contrast to this, and in light of increasing reports indicating spread of macrolide resistance, especially within the streptococcal species, we have concerns about the use of antibiotics for this non-antibiotic property. Therefore, we feel that use of erythromycin A as a prokinetic in the critically ill may not be justified and that the evidence for its beneficial effect needs to be weighed up against the risk of further emergence of antibiotic resistance associated with the increasing usage of macrolides.

Objectives of this review

The objectives of this review are the analysis of the data supporting the potential therapeutic benefit of erythromycin A compared with other alternatives such as metoclopramide as a prokinetic agent and the assessment of the risk of the potential concomitant contribution to the emergence of macrolide resistance.

As the starting point of our reasoning we will briefly: (i) outline the antimicrobial mode of action of and modes of antimicrobial resistance to erythromycin A and the other macrolides and ketolides, with particular emphasis on the streptococcal species and the Enterobacteriaceae as a reservoir of genetic elements encoding resistance; (ii) analyse the data demonstrating that increased use of macrolides contributes to the emergence of antibiotic resistance; and (iii) review the data supporting the potential therapeutic benefit of using erythromycin A against other alternatives such as metoclopramide as a prokinetic agent.

We will then comment upon what recommendations should be made upon its use as a first-line prokinetic versus other potentially available alternative agents in the critical care setting.

Summary of the antimicrobial action of erythromycin

Erythromycin A inhibits both formation of the 50S subunit and RNA-dependent protein synthesis in bacteria at the step of chain elongation by reversibly binding to the 50S ribosome subunit and blocking transpeptidation/translocation reactions. It can also inhibit messenger RNA (mRNA) translation at the level of the 23S rRNA (mostly interacting with domain V out of six domains I–VI) and ribosomal proteins L4 and L22, which are part of the 50S subunit. Erythromycin A can share common binding sites with other macrolides and other antibiotics, interfering with their binding to the ribosome. The macrolides mainly achieve inhibition of protein synthesis by binding in the exit tunnel of the ribosome where the evolving peptide is primarily formed by 23S rRNA. This tunnel is a dynamic structural component where interactions between the evolving peptide and the ribosome are taking place. These interactions influence the progression of synthesis as well as the activity of the ribosomal peptidyl transferase. The ribosomal proteins L4 and L22 form a constriction of the exit tunnel. Macrolides bind in close proximity to this constriction thus blocking the exit tunnel. It appears that the exact location of the protein synthesis inhibition seems to be dependent on the amino acid sequence of the evolving peptide. The ketolides such as telithromycin represent the most recent subgroup of the macrolide antibiotics. They demonstrate increased binding to the ribosome when compared with the older macrolides. The current understanding of the structure–activity relationship of the various macrolides has been reviewed in detail.

Macrolides are indicated for use as drug of choice for when ‘atypical’ pneumonia, such as that caused by Legionella pneumophila, is suspected. They are also an important alternative to penicillin in respiratory tract infections, infections caused by groups C and G streptococci, S. pneumoniae and S. pyogenes and for rheumatic fever prophylaxis. Consequently, they are extensively used drugs, especially in the treatment of streptococcal and respiratory tract infections. Ketolides retain activity against Gram-positive isolates resistant to erythromycin A and are also used in the treatment of respiratory tract infection. Owing to their different molecular structure, the target site of ribosomal interaction in ketolides differs from the other macrolides, hence they appear unaffected by some currently known mechanisms of resistance.

Mechanisms of macrolide resistance

Bacteria possess a huge and continuously evolving variety of resistance mechanisms to antibiotics. This review is concerned with the use of macrolides and their consequent impact on emergent resistances, particularly among streptococcal species, as they are pathogens that commonly cause infections for which macrolides are indicated. It has been reported that increased antibiotic pressure caused by macrolides may be linked with increased macrolide resistance in bacteria such as streptococci, but it is also important to understand the principle that emergence of new resistances in relation to the use of a certain antibiotic may not be limited purely to the group of antibiotics to which it belongs. Cross-selection can play a crucial role in the spread of resistant clones; for example, Karl Kristinsson has demonstrated that the abundant usage of co-trimoxazole in
Iceland has contributed to the spread of a penicillin-resistant clone of serotype 6 *S. pneumoniae.* It is also known that during the transfer of genetic material between isolates (including *S. pyogenes*), that genes conferring resistance to macrolides can be passed on in combination with other resistance genes [for example *tet(O)* conferring resistance to tetracyclines], resulting in multidrug-resistant isolates.

Several mechanisms of resistance to macrolides have been described, including efflux, methylation (23SrRNA), 23SrRNA/ribosomal protein mutations, esterase hydrolysis and inactivation by 2'-OH-phosphorylase/2'-OH-glycosidase. Streptococci possess many mechanisms by which they become less susceptible to the effects of macrolide (and other) antibiotics which include genes coding for methylases [erm(A), (B), (C), (F), (Q), (T)], ATP-binding transporters [msr(A) and msr(D)], efflux pumps [mef(A)] and transferases [lnr(C)]. Two resistance mechanism types account for almost all of the overall burden of resistance (in terms of MIC values and prevalence) to macrolides in streptococci and are discussed in more detail below.

**Efflux systems**

This resistance mechanism was first reported in 1996. Those possessed by streptococci tend to be coded for by *mef* (for macrolide efflux) genes, which are located on chromosomes, or on mobile genetic elements within the chromosome and mostly belong to the major facilitator (MF) superfamily, which is specific for 14- or 15-membered ring macrolides. The first described *mef* gene was found in *S. pyogenes* in 1996 and named *mef(A).* The *mef* gene found in *S. pneumoniae* was initially called *mef(E).* These two genes share 90% identity at the DNA level and at the time were detected using a PCR method that did not distinguish between the two variants. In 1999, Roberts *et al.* suggested that both genes should be referred to as *mef(A).* However, it has subsequently been shown that the two genes are carried by two different non-conjugative elements in *S. pneumoniae* and have disseminated differently among microbial species, prompting Klaassen and Mouton, in their recent minireview, to suggest that insight into the properties of the *mef* genes now acts in favour of maintaining the difference between *mef(A) and mef(E)* where efforts have been made to discriminate between them, for instance for *S. pneumoniae,* and to use the description *mef* when no efforts were made to distinguish between variants. Therefore, for future description in this review, we will refer to these genes and their variants as *mef.* The resulting resistance pattern against the 14- and 15-membered ring macrolides (including erythromycin, clarithromycin, roxithromycin and azithromycin) but not 16-membered ring macrolides, streptogramins or lincosamides, even after inducible expression can be distinguished from inducible methylesterases in Enterobacteriaceae may soon play a more significant part in the emergence of resistance.

**Summary of the prokinetic action of erythromycin A**

**Mode of action of erythromycin A on the gastrointestinal system**

Erythromycin A and other 14-membered ring macrolide antibiotics have a gastrointestinal motility stimulating effect; it has
been known for over 20 years that they act as a motilin receptor agonist in the gut and gallbladder stimulating enteric nerves and smooth muscle and triggering a phase of the migrating myoelectric complex.63,64 The antral motor effects of erythromycin A in humans are mediated via different pathways. The induction of a premature activity front is mediated through activation of an intrinsic cholinergic pathway, while the induction of enhanced antral contractile activity may be mediated via a pathway potentially involving activation of a muscular receptor.65 Different doses of erythromycin A may have different effects— as suggested in studies in patients with diabetic gastroparesis.14 Forty mg erythromycin A elicited a premature phase 3 complex that started in the stomach and migrated to the small intestine, while doses of 200 and 350 mg erythromycin A elicited a burst of antral phase-3-like contractions that did not migrate to the small intestine, but were followed by a prolonged period of antral contractile activity.

Risk versus benefits

Over the last decade, pharmaceutical companies have been investing significantly less in the development of new antimicrobial agents and we are currently facing a future where we will rely upon conserving the useful activity of our existing agents more than developing new agents in order to overcome or control the problem of resistance emergence. Therefore questions as follows need to be answered:

What is the epidemiology of the emergence of macrolide resistance?

There are many papers demonstrating that emergence of resistance to macrolides (which is often associated with co-resistance to other antibiotics) appears to be closely correlated to macrolide consumption.21–23,36,70,71 In the case of \( S.\ pneumoniae \), links with antibiotic use and resistance have been found at every ecological level,36 from individual patients69 to different geographical regions70 and countries.71 Overall consumption of macrolides has been shown to vary significantly between European countries. Studies done by the European Surveillance of Antimicrobial Consumption (ESAC) Project Group,72 reveal that total national macrolide use [expressed in defined daily doses (DDD) per 1000 inhabitants per day] in 2003 was 0.85 in Sweden compared with 9.36 in Greece. They also reveal that macrolide consumption continues to increase in some countries including Portugal, Ireland, Finland, Denmark and especially Greece, where there has been a dramatic increase in total macrolide consumption from 4.16 DDD/1000 inhabitants/day in 1997 to 9.36 in 2003. Another study by the ESAC Project Group adds further weight to the concerns over increasing antibiotic consumption and alarming resistance rates by showing a correlation between antibiotic resistance and outpatient antibiotic use in Europe.23 Clonality and related mechanisms of macrolide resistance in \( S.\ pneumoniae \) have been reported recently. The authors observed that common clones are shared between Europe, Asia and America, with clustering within countries.73 As demonstrated repeatedly, rates of resistance and phenotype vary widely between geographical areas and are affected by many factors, not all of which are fully understood. They include different antibiotics exerting different selective powers and local spread of resistant or susceptible clones, in addition to those factors influencing antibiotic consumption, e.g., genetic, cultural, sociological and public health factors.36 Felson and colleagues found rates of resistance to erythromycin A of up to 87.6% in \( S.\ pneumoniae \) in South Korea compared with 4.7% in Sweden.71 Other studies demonstrate differences in the prevalence of phenotypes; one study of invasive pneumococcal isolates in Germany revealed that 56.1% of macrolide-resistant isolates were of the M phenotype (43.4% MLS\( \beta \)) compared with a Belgian study74 with 9.1% M phenotype macrolide-resistant \( S.\ pneumoniae \) isolates. Similar findings regarding the variance in resistance rates and phenotypes have been found in isolates of \( S.\ pyogenes \) and also in viridans group streptococci.24,50,51,79–81

In the past decade macrolide resistance has rapidly increased, exceeding resistance rates to \( \beta \)-lactam antibiotics in some parts of the world in the case of clinical \( S.\ pneumoniae \) isolates.82 National surveillance in Germany revealed an increase in erythromycin A resistance in pneumococcal isolates from 3.0% in 1992 to 15.3% in 2000, thought to be driven by uncritical usage of macrolides. The authors warned that broad usage of macrolides ought to be reconsidered.25 Another American surveillance study also concurred with the rapid increase in the numbers of macrolide-resistant pneumococcal strains.83 However, a Canadian surveillance study notes that their prevalence of macrolide resistance in \( S.\ pneumoniae \) isolates has remained stable at around 8% between 1997 and 2000 despite large increases in macrolide consumption.84 This was thought to have occurred secondary to the total use of antibiotics in Canada decreasing over this period. There is controversy concerning the clinical significance of in vitro macrolide resistance as few patients with clinical failure have been reported.85 However, the study by Gay et al.83 showed that the increase in high-level macrolide resistance in Atlanta was almost exclusively of a \( \text{mef} - \text{mediated type} \), which was associated with higher MICs whereas \( \text{erm} - \text{mediated resistance remained stable} \). They postulate that this may lead to an increase in clinical failures. Overall, studies tend to suggest a correlation between macrolide resistance and clinical failure, although further studies are needed to assess the in vivo impact of in vitro resistance.

What is the evidence for conditions promoting bacterial resistance against macrolides?

It is known that dose and therefore tissue levels achieved have an effect on the ability of microorganisms to select for resistance under antibiotic pressure.69 Both the MLS\( \beta \) and M phenotypes have been described among pathogens such as \( S.\ pneumoniae \) and \( S.\ pyogenes \) in addition to the viridans group streptococci that comprise the normal oropharyngeal flora in the healthy population. Also, further resistance mechanisms are emerging—a novel efflux system in \( S.\ pyogenes \) not associated with \( \text{mef}(A) \) or other known macrolide efflux genes has been described and found to be transferable between strains of \( S.\ pyogenes \).86

The viridans group streptococci are thought to play a significant role in the spread of macrolide resistance. Antibiotic pressure with macrolides increases the prevalence of erythromycin-A-resistant viridans group streptococci; it is well known that resistance rapidly emerges among oral streptococci in patients.
treated with erythromycin A and this effect appears to last at least up to 8 weeks after the antibiotic pressure is removed. Rates of pharyngeal carriage of resistant commensal streptococci are as high as 94.4% in a population comprising both healthy subjects and those suffering pharyngitis. Worryingly, the intragenic transfer of macrolide-resistant determinants is possible and it is likely that genes such as erm and mef will spread into new species. Transfer of genes coding for mechanisms of resistance to macrolides has been demonstrated between isolates of *S. pyogenes* and between isolates of *S. pneumoniae* and from viridans group streptococci isolates to pathogenic isolates such as *S. pyogenes* and *S. pneumoniae*. The predominance of the same resistance determinants found in both commensal bacteria and pathogens suggests the genetic transfer of resistance determinants. Seppälä et al. demonstrated that the distribution of phenotypes among the viridans streptococci resembles that found in *S. pyogenes*, with predominance of the M phenotype and that the gene coding for the MLSB phenotype, erm(B), is the same in viridans streptococci as in *S. pneumoniae*. These results emphasize that these components of our oropharyngeal flora may act as a reservoir of resistance genes by providing a pool of resistant bacteria that may transfer resistance determinants to more pathogenic organisms.

Emergence of macrolide resistance is not only limited to streptococci. For example, it has been shown to arise during eradication treatment of *Helicobacter pylori* from the stomach mucosa, often in combination with another antimicrobial agent and a proton pump inhibitor and seems to be secondary to rRNA mutations. Consequently, the rate of macrolide resistance in *H. pylori* may cause therapeutic problems in the future.

Similar to the upper respiratory tract, the human colon has long been demonstrated to be an ideal environment for both the inter- and intra-species transfer of macrolide resistance. Twenty years ago, the acquisition of the plasmid-mediated gene *ere* expressing an esterase leading to high-level resistance to erythromycin A in *Escherichia coli* had already been reported. Before that, the organism only expressed low-level intrinsic resistance to macrolides. In another study, the conjugative plasmid pPI100 encoding ampicillin and gentamicin resistance in addition to erythromycin A resistance was isolated from the blood of a patient treated with erythromycin. At the time, oral erythromycin A was used for selective gut decontamination of Enterobacteriaceae on the basis that the intraluminal concentrations achieved substantially exceeded the MICs of these organisms. When investigating the epidemiological aspects of using erythromycin A for selective gut decontamination, the authors demonstrated that individual exposure to erythromycin, rather than cross-infection, resulted in the emergence of Enterobacteriaceae expressing high-level resistance to erythromycin. Later it could be demonstrated that the relevant genes, *ere*(A) and *ere*(B), encoding for two distinct erythromycin A esterases, and *erm*(AM), encoding for a rRNA methylase, were already disseminated amongst other species of the Enterobacteriaceae. A variant of *ere*(A) has been found in an integron cassette of a multiresistant strain of *Providencia*. The transferability of plasmid pPI100 was also investigated in a mouse model. The authors found in a gnotobiotic mice model that transferability was antagonized in the presence of the anaerobic flora of the human gut. This observation is of particular interest in respect of the intensive care setting where patients often require anti-anaerobe chemotherapy, hence the transfer of resistance is likely to be fostered this way. However, the anaerobic gut flora has been shown to participate in the exchange and accumulation of genetic elements encoding for erythromycin A resistance. In their survey, Shoemaker et al. found that six strains of *Bacteroides* spp. had acquired an *erm*(B) gene, which turned out almost identical to *erm*(B) from *Clostridium perfringens*, *S. pneumoniae* and *Enterococcus*. Furthermore, an erythromycin A resistance gene from a conjugal *Bacteroides* spp. transposon has been found to be almost identical to *erm*(G) from *Bacillus sphaericus*, a Gram-positive bacterium usually found in soil.

Another topical concern has been the spread of a toxigenic strain of *Clostridium difficile* PCR ribotype O27 particularly affecting hospitals in North America and the UK. A recent study into the rates of resistance to commonly used antibiotics in clinical isolates of *C. difficile* from symptomatic hospital patients has shown that resistance rates to erythromycin A were as high as 98% and 100% for the two most commonly occurring PCR ribotypes (001 and 006 respectively). There is an MLS resistance gene designated *erm*(BZ) associated with toxigenic *C. difficile* and transfer between *C. difficile* strains has been demonstrated. The investigators found that the element responsible for gene transfer was characteristic of a conjugative transposon, was found in six *C. difficile* strains and could be transferred to a non-toxigenic *C. difficile* strain demonstrating that exposure of gut organisms to antibiotics not primarily intended for their eradication promotes horizontal gene transfer. Further evidence was found by researchers in the Netherlands when investigating the sudden increase in multidrug-resistant Enterobacteriaceae. They identified a number of integrons, one of which also conferred erythromycin resistance. Conjugation experiments supported the epidemiological evidence of horizontal transfer of resistance genes.

Rice reviewed the same aspect for the Gram-positive bacteria concluding that common Gram-positive pathogens are able to associate and propagate antimicrobial resistance genes. When evaluating the composition of a number of transposable genetic elements, Rice also found compelling evidence that as a result of high exposure to antimicrobials, bacteria are able to associate insertion sequence elements with resistance genes thus generating novel integrative elements conferring resistance. Genomic data suggest that this ancient ability proved to be an essential tool for the bacterial evolutionary process. Therefore it can be concluded that the extensive use of antibiotics in the clinical setting is placing the bacterial community under selective pressure resulting in the application of ‘ancient evolutionary tools’ in order to develop protective mechanisms for survival under those circumstances. Recent research suggests that a process called ‘modular evolution’ may enable bacteria to retain horizontally acquired genes even once they do not provide a selective advantage anymore.

What is the clinical role for prokinetics?

To date, the use of prokinetic agents for improvement of gastric emptying has been investigated in a range of clinical settings outside that of the critical care unit and these are beyond the scope of this article. For example, erythromycin A shortened the prolonged gastric-emptying times for both liquids and solids to normal in patients with insulin-dependent diabetes mellitus and gastroparesis suggesting that it may have therapeutic value.
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in patients with severe diabetic gastroparesis.\textsuperscript{11,14} It has also shown potential benefit in other areas, including patients after vagotomy\textsuperscript{11} and patients with chronic intestinal pseudo-obstruction.\textsuperscript{112}

One area where this application could have a particular impact is in the critical care setting. Successful and early administration of enteral nutrition is integral to improving clinical outcome; resulting in fewer septic complications, decreased bacterial gut translocation and catabolic response to injury and improved wound healing.\textsuperscript{113–115} However, numerous studies evaluating gastrointestinal motility by measuring acetaminophen absorption and performing manometry and breath testing have shown that this is frequently impaired in the critically ill, with decreased gastric emptying and diminished migrating motor complexes.\textsuperscript{116–119} Slow gastric emptying, or gastroparesis, is a major limitation in mechanically ventilated patients and, in addition to impairing the absorption of nutrients and drugs, can lead to complications directly related to enteral feeding, such as bacterial overgrowth and oesophageal reflux. Such complications place these patients at risk of pulmonary aspiration, pneumonia and sepsis, which in turn impacts on mortality.\textsuperscript{120} Prokinetic agents may improve tolerance to enteral nutrition by overcoming gastrointestinal dysmotility.\textsuperscript{115,121} Their usefulness in the critical care population has been reviewed.\textsuperscript{18,122} This class of drugs (which includes the non-antibiotics in addition to erythromycin) was found to have a beneficial effect on gastrointestinal motility as measured by endpoints such as gastric residuals, acetaminophen absorption as a surrogate marker and manometry in certain situations during enteral feeding. However, it is recognized that the number and sample sizes of clinical trials in this area are small and that finer details such as the ideal doses of the drugs are yet to be established. Only one randomized trial of motility agents to date has assessed their impact on clinical outcomes including incidence of pneumonia and mortality rate\textsuperscript{123} and it did not show any benefit of the prokinetic over placebo.

What is the clinical evidence for erythromycin A as a prokinetic agent?

So far there are no studies that have investigated the impact of erythromycin A use upon clinical endpoints in critical care patients. Two studies have shown that erythromycin A increases the success rate of small-bowel-feeding-tube placement (and shortens procedure time) compared with placebo,\textsuperscript{124,125} although another study did not find any significant advantage of erythromycin A over metoclopramide in this setting and in fact concluded that motility agents given prior to tube insertion do not augment advancement of the feeding tube beyond the stomach and may in fact hinder placement into the duodenum.\textsuperscript{126}

Booth et al.\textsuperscript{18} found only two small studies in their review investigating the effects of erythromycin A compared with placebo on gastrointestinal transit and feeding tolerance – with sample populations ranging from 10 to 20.\textsuperscript{17,127} Their findings suggested that erythromycin, when using acetaminophen as a surrogate marker, increased its absorption and antral contractions, reduced residual volumes, did not have a significant effect on gastric microbial overgrowth\textsuperscript{128} and was associated with patients being categorized as ‘successful feeders’. However, another larger placebo controlled trial of 40 consecutive patients demonstrated that erythromycin A promoted gastric emptying only for the first 3 days of enteral feeding but that it had no significant effect on residual volumes after this time.\textsuperscript{129}

What alternative prokinetic agents are available?

Erythromycin A is not the only agent with prokinetic properties. A variety of agents have been considered and investigated for use as prokinetics. Although alternative agents are limited, there are some that are clinically available. Outlined below are some of those that have been in clinical use or are being developed for clinical use. Despite the paucity of published and robust clinical trials, where possible, we have reviewed the current literature for evidence of each agent’s effectiveness within the critical care setting and performance against erythromycin.

Metoclopramide. This drug promotes gastric emptying by acting as an antagonist to the inhibitory actions of dopamine in the gut.\textsuperscript{121} It also sensitizes the gut to acetylcholine and increases the lower oesophageal sphincter tone.\textsuperscript{122} The review by Booth et al.\textsuperscript{18} concluded that administration of metoclopramide appears to increase physiological indices of gastrointestinal transit and feeding tolerance. As yet, there is no consensus upon the appropriate dose to use and 20 mg appears to be no more efficacious than 10 mg.\textsuperscript{122}

Few placebo comparison studies have been done and those that do exist are of small sample size. One crossover study of 10 patients comparing the effect of one dose of 10 mg intravenous metoclopramide with intravenous saline upon the physiological outcome of acetaminophen absorption concluded it improved gastric emptying,\textsuperscript{130} as did the small study by Calcroft et al.\textsuperscript{131} Another similar study\textsuperscript{132} (eight patients, one dose via the nasogastric tube of each prokinetic and placebo per patient) found 10 mg metoclopramide via the nasogastric tube had no significant effect over placebo on mean residence time of acetaminophen absorption (the same was found with 200 mg erythromycin A versus placebo), but did tend to accelerate absorption once it had started to occur. They found erythromycin A did not have this effect. In the context of usefulness of metoclopramide over placebo in feeding tube placement, one small study using 20 mg iv\textsuperscript{133} concluded it aided placement when given prior to tube insertion while studies using 10 mg iv\textsuperscript{126,134,135} concluded it did not. Only one large randomized trial has assessed the impact of prokinetic use in the critically ill on clinical outcomes including incidence of pneumonia and mortality rate.\textsuperscript{123} Metoclopramide (10 mg given via a nasogastric tube) was the only drug studied and it did not show any clinical benefit over placebo.

We have found two studies on critically ill patients that include both metoclopramide and erythromycin. The MacLaren study\textsuperscript{132} above found that metoclopramide was significantly better at shortening the mean residence time for acetaminophen absorption and also for accelerating gastric emptying in critically ill patients and a larger, methodologically robust study found that neither metoclopramide nor erythromycin A augment the advancement of a feeding tube beyond the stomach.\textsuperscript{126}

Lastly, as part of their review into nutrition support in mechanically ventilated, critically ill adult patients, the Canadian Critical Care Practice Guidelines Committee have recommended that given the low probability of harm and favourable feasibility, motility agents may be considered to optimize
Domperidone. Like metoclopramide, this drug is another dopamine receptor antagonist, mediating the inhibitory action of dopamine on the upper gastrointestinal tract. However, it is a chemically distinct dopamine2-antagonist and unlike metoclopramide it acts peripherally. The clinical role of domperidone in critically ill patients with gastrointestinal dysmotility has not been established and there are no published studies. It has however been extensively studied\textsuperscript{138} in other clinical scenarios such as diabetic gastroparesis,\textsuperscript{139} functional dyspepsia\textsuperscript{140,141} and gastro-oesophageal reflux disease (GORD).\textsuperscript{141} A review of the literature on the effect of domperidone on symptomatic relief to treatment found that domperidone provided better relief from symptoms than placebo and was comparable to metoclopramide in patients with diabetic gastropathy and dyspepsia and promising outcomes were also seen in trials reviewing GORD.\textsuperscript{138} The same reviewer noted that, as, unlike metoclopramide, domperidone does not readily cross the blood–brain barrier, it is less likely to cause the central nervous system adverse effects (e.g. dystonic reactions and dizziness) seen occasionally with metoclopramide. Therefore it may become a useful therapeutic alternative to other prokinetic agents in critical illness. Further studies are needed.

Tegaserod. Tegaserod is a selective serotonin type 4 receptor partial agonist. The activation of the 5-hydroxytryptamine\textsubscript{4} (5-HT\textsubscript{4}) receptors results in the activation of the peristaltic reflex and an increase in intestinal secretions.\textsuperscript{142} It is licensed in Canada for the relief of irritable bowel syndrome symptoms such as constipation, abdominal pain and bloating. It is not currently in use in the UK. No studies have been published, although there are case reports of its successful use in intensive care patients with impaired gastric motility.\textsuperscript{143} Further studies are needed.

Cisapride. Promotes motility by activating 5-HT\textsubscript{4} receptors, thus enhancing acetylcholine release in the enteric plexus\textsuperscript{121} and initiating the gastric peristaltic reflex. It has been found to accelerate gastric emptying as assessed by acetaminophen absorption in patients with idiopathic and diabetic gastroparesis\textsuperscript{144,145} and also in critically ill patients.\textsuperscript{146,147} It was withdrawn from the market in the UK in May 2000 over concerns regarding cardiac dysrhythmias.

Motilin receptor agonists ‘motilides’ (ABT-229). ABT-229 is a specific motilin agonist that dose-dependently accelerates gastric emptying.\textsuperscript{148} It has been studied in patients with functional dyspepsia and diabetic gastroparesis,\textsuperscript{148,149} but results so far have been disappointing with no significant symptom improvement seen.\textsuperscript{150} Drug factors such as tachyphylaxis may have played a role in therapeutic failure.

Conclusions

We find that today we live in a world where there are already areas with a high prevalence of erythromycin A resistance within our populations; whether that is the healthy adult population (with a study finding oropharyngeal carriage rates of 70% in Belgium\textsuperscript{51} and another finding rates of 94% in Spain\textsuperscript{24}) or in organisms regarded as pathogens. In view of this, and the decline in the development of novel antimicrobial agents, the decision of which clinical situations it is appropriate to use antibiotics in becomes critical. We agree with Goossens et al. in that the ethics of promoting antibiotics in clinical situations in which they are unnecessary should be given serious consideration.\textsuperscript{23}

The use of erythromycin A at doses far below the concentrations necessary for an inhibitory effect on susceptible bacteria provides close to ideal conditions for the induction of bacterial mutation and selection,\textsuperscript{151,152} which is the type of situation achieved at some of the doses of erythromycin A proposed for use as a prokinetic.\textsuperscript{17,22,124,126,127}

We already know that increased antibiotic pressure can create an environment suitable for the emergence of macroide resistance and that it is potentially possible for resistance genes associated with mobile genetic elements to facilitate spread of resistance in oropharyngeal flora and among invasive clinical isolates. These factors are especially important when applied to the closed environment of the critical care unit, where resistant organisms have the ability to become ‘resident’\textsuperscript{153} or cause outbreaks,\textsuperscript{154,155} posing a risk to patients on the unit.

In the critically ill population prokinetics have been proposed to have a beneficial effect. However, the evidence so far is based on a small number of studies, which importantly have not been able to consistently concur on doses and length of time needed for optimum prokinetic effect and include few on actual clinical outcome measures. Indeed, some studies (including the one measuring clinical endpoints) are conflicting and unable to prove that prokinetics even have a significant beneficial effect, although this may be because larger studies are needed.

The evidence for the use of macrolides such as erythromycin A as a first-line treatment of a non-septic condition such as gastrointestinal dysmotility in the critical care population is weak. In fact, the American Society for Parenteral and Enteral Nutrition (ASPEN) states explicitly that, because of the concerns about the emergence of bacterial resistance, only metoclopramide should be used.\textsuperscript{136} In their recent guidelines, the European Society for Clinical Nutrition and Metabolism (ESPEN) goes even further by not recommending the use of erythromycin A or another prokinetic agent at all.\textsuperscript{156}

On balance, we conclude that current evidence is not complete enough to be able to state that one prokinetic agent, e.g. erythromycin, is superior to another, e.g. metoclopramide, in the critical care setting.\textsuperscript{18,130,132,157} In view of this, the use of erythromycin A as a first-line agent for the treatment of gastric dysmotility in the critically ill lacks sufficient data to justify taking the risks of promoting the spread of macrolide resistance. Owing to the growing weight of evidence illustrating the potential epidemiological impact of increased and wider usage of erythromycin A and its fellow macrolides upon both the emergence of antibiotic resistance and its genetic determinants’ ability to transfer and collect within the bacterial flora of both patients and healthy individuals in the general population, we are of the opinion that the use of erythromycin A as a prokinetic agent in the critical care unit should be restricted to only those patients who have already failed all other treatments for impaired gastric motility and are intolerant of a first-line agent such as metoclopramide. In our own hospital there is an agreement within the
Intensive Care Team that erythromycin A should only be used as a prokinetic in exceptional circumstances.

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Transparency declarations

None to declare.

References


Review


Review


